

*Clodoveo Ferri*

Overview of the Research Line:  
***from Mixed Cryoglobulinemia***  
***(Cryoglobulinemic Vasculitis)***  
***to HCV infection, Autoimmunity, and Oncogenesis***

## Summary

Since the early seventies, Prof. Clodoveo Ferri has conducted numerous clinical and etiopathogenetic studies on a large Italian case series of patients with mixed cryoglobulinemia (MC), synonym cryoglobulinemic vasculitis (CV), in close collaboration with Prof. Stefano Bombardieri and Gianpiero Pasero and numerous other Italian and foreign experts.

Starting from MC, the overall body of researches includes (see Figure and comments on page 5 and 6):

1970s-1980s -> clinical-immunological studies on cryoprecipitation, hepatic, renal, neurological and pulmonary involvement of MC, role of 'indolent' lymphoproliferation underlying cryoglobulinemic syndrome

**1991** -> first demonstration of the close association between hepatitis C virus infection and MC by HCV RNA detection

1993 -> studies on HCV lymphotropism, which in addition to its hepatotropism is able to infect and stimulate (over-expression of Bcl2) peripheral lymphocytes in patients with HCV-associated MC

**1994** -> first demonstration of a significant association between HCV infection and 'idiopathic' B-cell NHL

in the following years -> numerous studies focused on the role of HCV in various immune-mediated disorders, organ- and non-organ-specific (thyroid, pancreas, porphyria cutanea tarda, etc.), as well malignancies (papillary thyroid carcinoma, in addition to B-NHL and hepatocellular carcinoma)

moreover: survival studies on MC pts, diagnostic and therapeutic guidelines, and more recently the evaluation of the impact of the COVID-19 pandemic on 450 patients with MC.

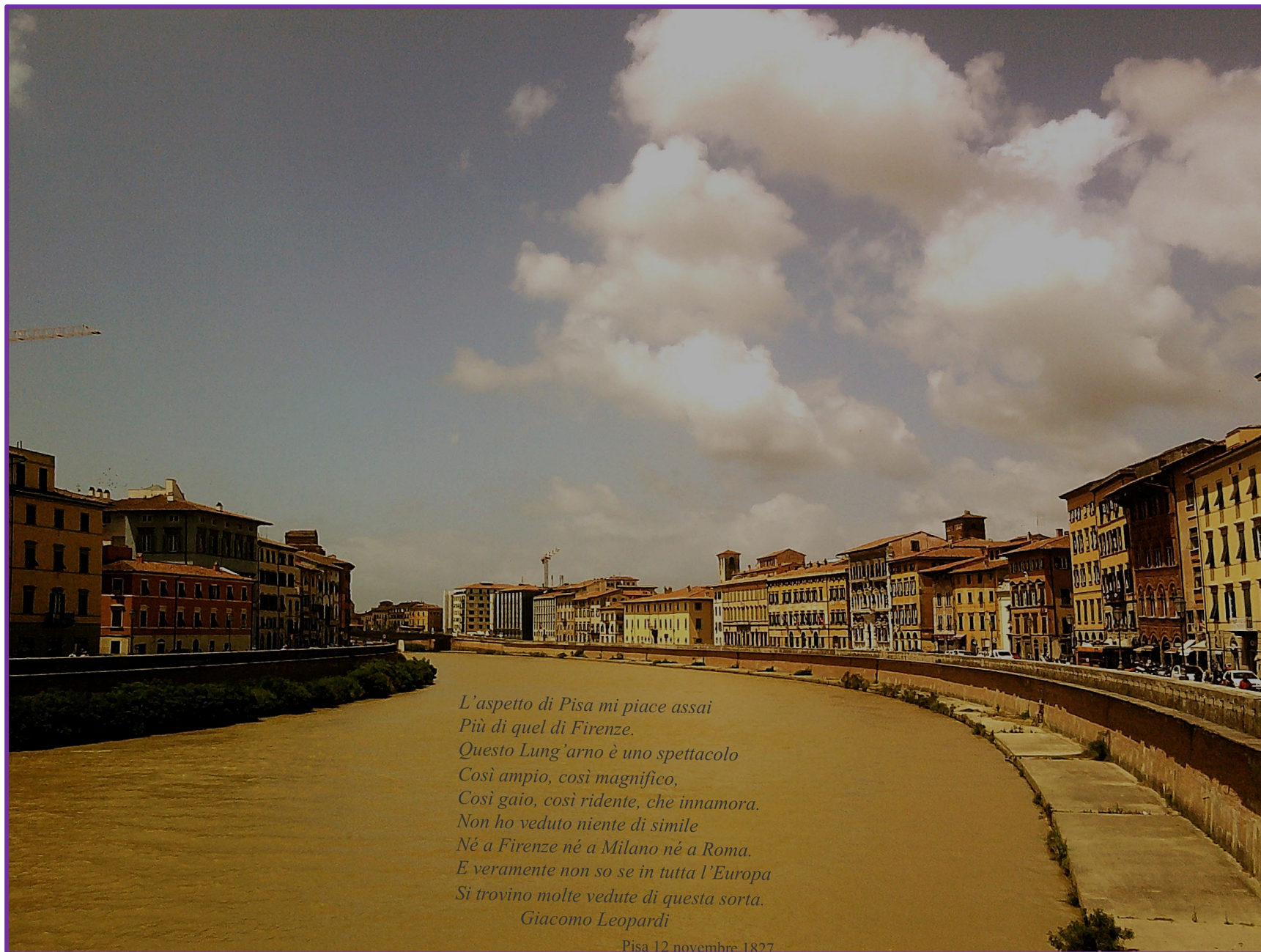
**The long research activity for over 50 years** has produced a large body of knowledge and pioneering studies, also thanks to fruitful collaborations with other recognized experts.

The history of MC starts from the early decades of the 20th century, initially as well-known 'laboratory curiosity', the immuno-cryoprecipitation, associated with seropositivity for rheumatoid factor (RF) and complement consumption; these serological abnormalities, very often without apparent clinical significance, only in some subjects lead to the **clinical triad arthralgia/asthenia/vasculitic purpura**. The presence of these symptoms, including serum FR+, suggested a specific clinical syndrome well codified in the 1960s by Meltzer M and Franklin EC (Am J Med. 1966). In the absence of known causes/clinical associations in the majority of patients the **MC syndrome** was classified as 'essential'.

The numerous clinical-pathological facets of the MC syndrome have suggested a series of studies in different fields, involving, in addition to rheumatologists, various specialists, such as virologists, internists, immunologists, hematologists, hepatologists, nephrologists, neurologists, etc.

**The results of researches recorded so far are of great relevance for various aspects, in particular:**

- **biological field:** the demonstration of etiopathogenetic link underlying the symptomatic complex 'Infection-autoimmunity-lymphoproliferation-cancer'
- **clinical practice:** the eradication of the common viral triggering agent (HCV) can lead in many subjects to the remission of the autoimmune-vasculitic syndrome and/or malignant lymphoproliferation.



*L'aspetto di Pisa mi piace assai  
Più di quel di Firenze.  
Questo Lung'arno è uno spettacolo  
Così ampio, così magnifico,  
Così gaio, così ridente, che innamora.  
Non ho veduto niente di simile  
Né a Firenze né a Milano né a Roma.  
E veramente non so se in tutta l'Europa  
Si trovino molte vedute di questa sorta.  
Giacomo Leopardi*

Pisa 12 novembre 1827

### *The Lungarni of Pisa*

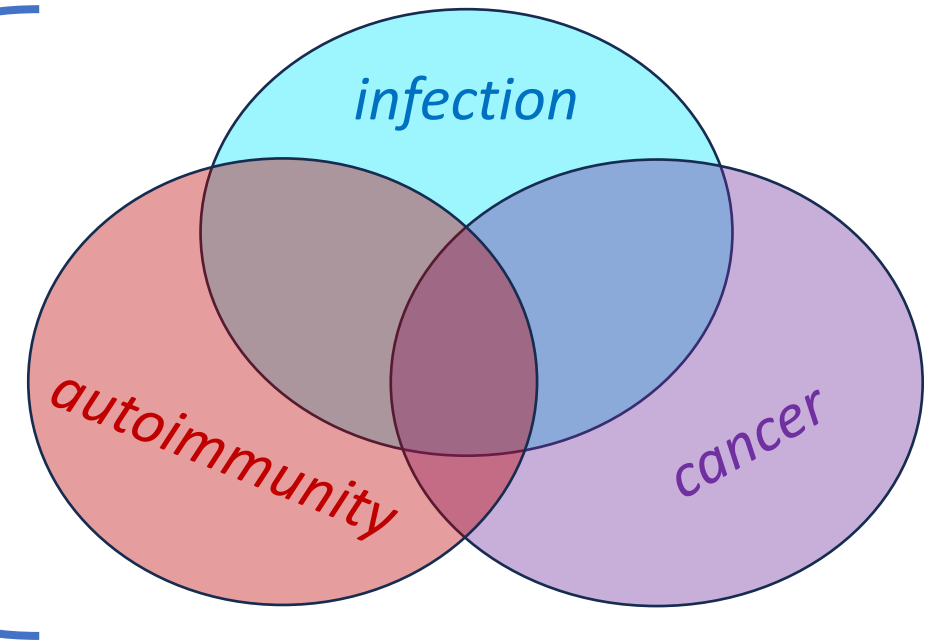
*I like the look of Pisa much  
more than that of Florence.  
This Lungarno is a spectacle  
so large. so magnificent,  
so gay. so smiling. that it makes you fall in love.  
I have seen nothing similar  
neither in Florence nor in Milan nor in Rome.  
And I really do not know if in all of Europe  
one finds many views of this kind.*

*Giacomo Leopardi*

*Pisa 12 novembre 1827*

*Mixed Cryoglobulinemia & HCV  
a model of  
infection, autoimmunity, and oncogenesis*

The history of this  
multistep research line,  
moving towards  
different directions,  
may be useful  
for many aspects,  
in particular



- *it may have a stimulating and educational value, especially for students, young researchers, and clinicians*
- *it underlies the relevance in the clinical practice to deal with the complexity requiring a multidisciplinary approach*

## Editorial

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# **Mixed cryoglobulinaemia and hepatitis C virus: a paradigm of a virus-related autoimmune and lymphoproliferative disorder**

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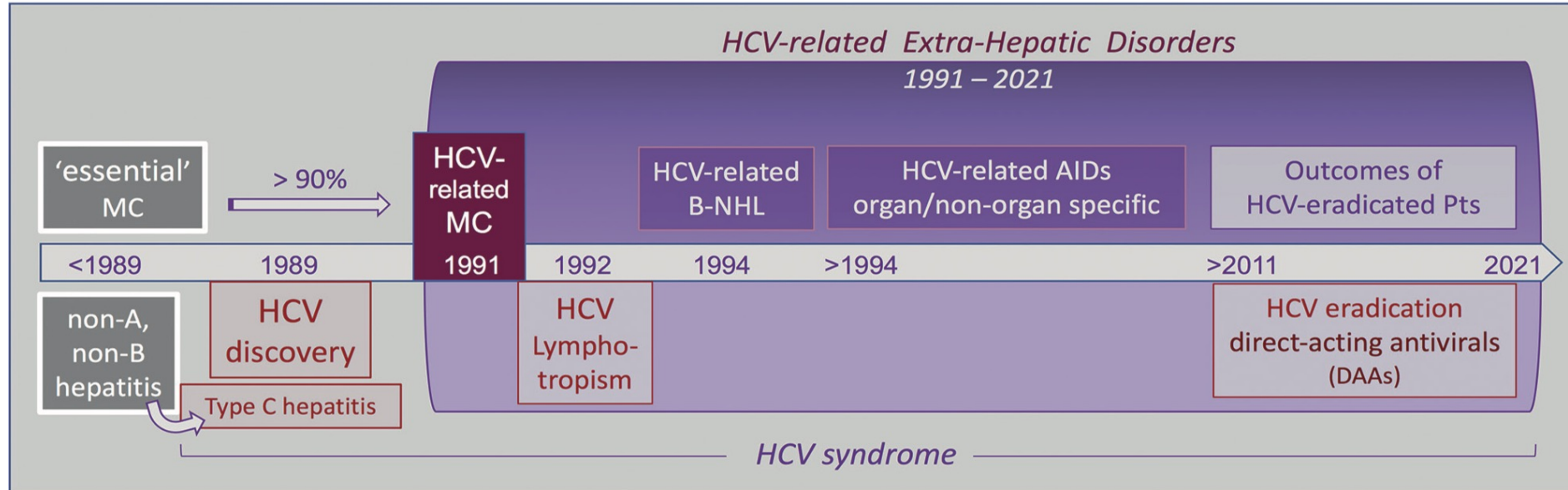
C. Ferri<sup>1</sup>, S. Bombardieri<sup>2</sup>

*Clin Exp Rheumatol 2021; 39: 1265-1268.*

# multistep process

## Mixed cryoglobulinaemia and hepatitis C virus: a paradigm of a virus-related autoimmune and lymphoproliferative disorders

Ferri C, Bombardieri S  
Clin Exp Rheumatol 2021



**Fig. 1.** Schematic representation of thirty-year history of HCV-related mixed cryoglobulinaemia and other HCV-related extra-hepatic disorders (HCV-EHDs). Following the **HCV discovery (1989)**, the striking **association between HCV and mixed cryoglobulinaemia (MC)**, synonymous with cryoglobulinemic vasculitis, was **demonstrated in 1991**. Both dates represent a fundamental turning point in the history of two disorders previously classified of unknown aetiology: the so-called non-A, non-B hepatitis and the 'essential' MC. The association HCV-MC opened a fruitful succession of clinical-epidemiological, virological, and pathological studies that over the last three decades led to the definition of HCV-related extra-hepatic disorders (HCV-EHDs), **a complex of autoimmune organ- and non-organ-specific, and lymphoproliferative disorders, mainly B-cell non-Hodgkin lymphoma (B-NHL)**.

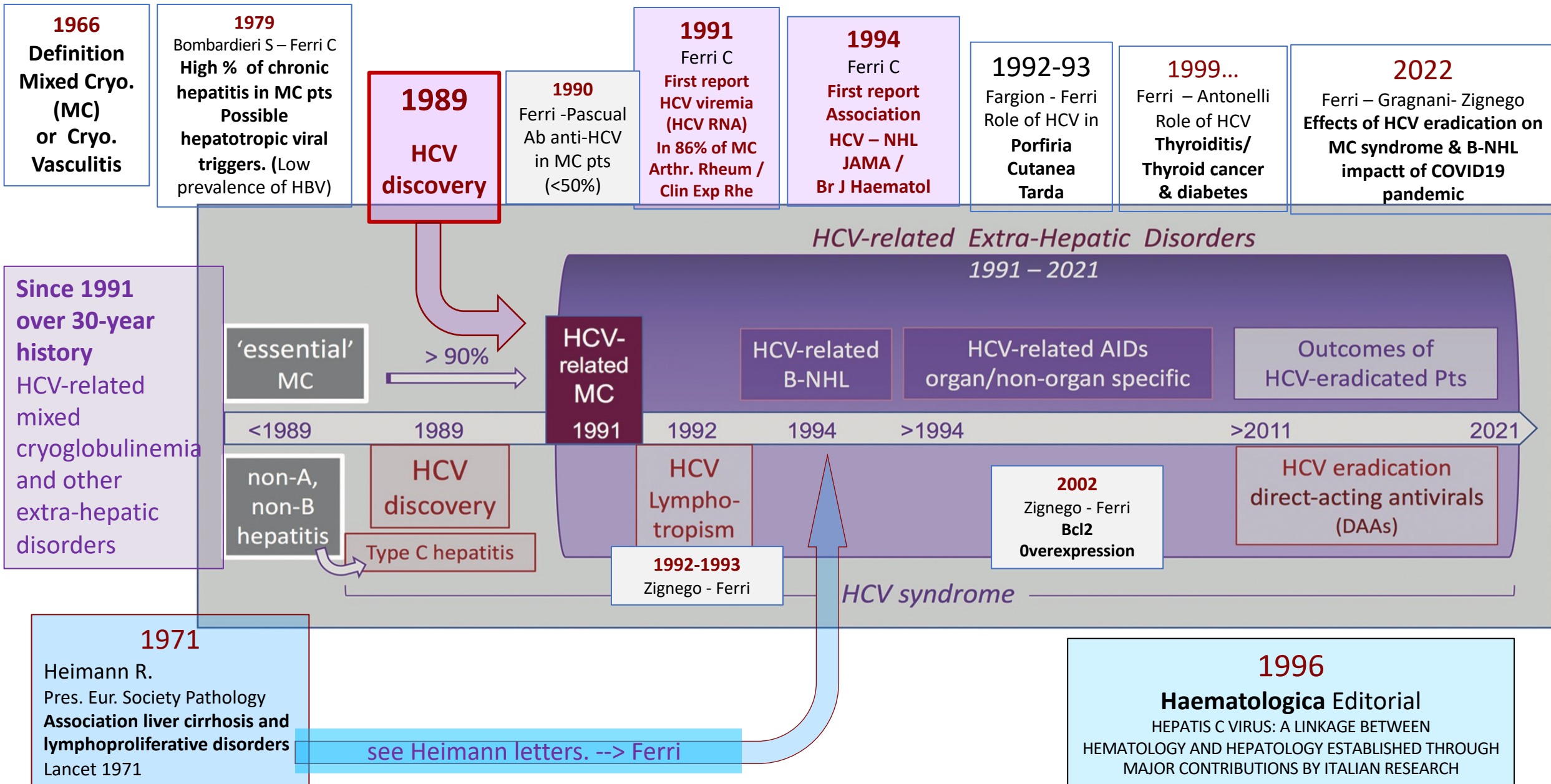
HCV syndrome' consists of the aggregation of

- HCV-related hepatic manifestations (hepatitis C, cirrhosis, hepatocellular carcinoma) and
- HCV extra-hepatic disorders: MC syndrome, B-NHL, endocrine disorders, porphyria cutanea tarda, etc.

More recently we are experiencing another revolution following the introduction of direct-acting antivirals (DAAs), able to eradicate the HCV. However, many issues still remain open, especially as regards the persistence or relapses/flares of different HCV-EHDs, mainly the cryoglobulinaemic vasculitis and B-NHL despite HCV eradication.

from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis) to HCV infection, Autoimmunity, and Oncogenesis.  
1972 -2024

# *multistep process*





Ionian Sea



# From internal medicine to rheumatology and back: the example of mixed cryoglobulinemia

*Pasero GP, Bombardieri S, Ferri C*  
Clin Exp Rheumatol 1995 Jan-Feb;13(1):1-5.

**Seventies-Eighties**

## First key observation

- **High prevalence of liver involvement in patients with mixed cryoglobulinemia**  
(from chronic hepatitis to cirrhosis/hepatocellular carcinoma)  
Of note, liver involvement is a rare complication in the course of other systemic vasculitides
- **This finding suggested a possible causal role of ‘hepatotropic’ infectious agent(s) in patients with mixed cryoglobulinemia**

## Seventies-Eighties

- **The high prevalence of liver involvement** (from chronic hepatitis to cirrhosis, and hepatocellular carcinoma) in patients with mixed cryoglobulinemia or cryoglobulinemic vasculitis (of note, chronic hepatitis is a rare organ complication in the course of other systemic vasculitides) **suggested the possible causal role of a 'hepatotropic' infectious agent.**
- **HBV** could represent a likely candidate also in light of its role in patients affected by another form of systemic vasculitis, the polyarteritis nodosa, described since the early seventies.
- However, the **low prevalence of HBV infection in patients with mixed cryoglobulinemia** (with/without chronic hepatitis) led to exclude its role in the majority of patients.
- **Before the discovery of HCV (1989), many 'idiopathic' hepatitis were classified as 'nonA, nonB hepatitis' and mixed cryoglobulinemia as 'essential' MC**  
(see figure page 7 & 8)

*Ric Clin Lab* 1979

### **Liver involvement in essential mixed cryoglobulinemia**

[S Bombardieri](#), [C Ferri](#), [O Di Munno](#), [G Pasero](#)

#### **Abstract**

Twenty-one of 30 patients with essential mixed cryoglobulinemia (EMC) had evidence of liver involvement.

The liver disease was characterized by the absence of clinical symptoms, hepatosplenomegaly, mild elevation of enzymes, abnormal BSP retention and low albumin levels. Histology, available in 12 patients, showed either chronic persistent or chronic active hepatitis or liver cirrhosis; 44% of the patients had HBsAg or HBsAb in sera and/or cryoglobulins, confirming the high frequency of exposure to hepatitis B virus (HBV) infection in EMC. However, liver lesions were similar in all patients, regardless of HBV exposure. Since other factors usually associated with chronic liver diseases were absent or apparently irrelevant, it is tempting to speculate that a 'cryoglobulinemic hepatitis' may exist as a distinct syndrome. The characteristic complement profile of the patients with EMC (low CH50 and C4, normal C3PA), not related to albumin levels, can help to differentiate this disease from chronic liver disease without cryoglobulins.

Soon after the discovery of HCV (1989), as the main cause of non-A, non-B hepatitis, **in 1990 two preliminary observations** on a limited number of patients with Mixed Cryoglobulinemia highlighted the presence of serum antibodies (detected by first generation RIBA) However, the increased prevalence of anti-HCV remained less than 50% of patients

1990

-**Pascual M et al**, Hepatitis C virus in patients with cryoglobulinemia type II. *J Infect Dis* 1990

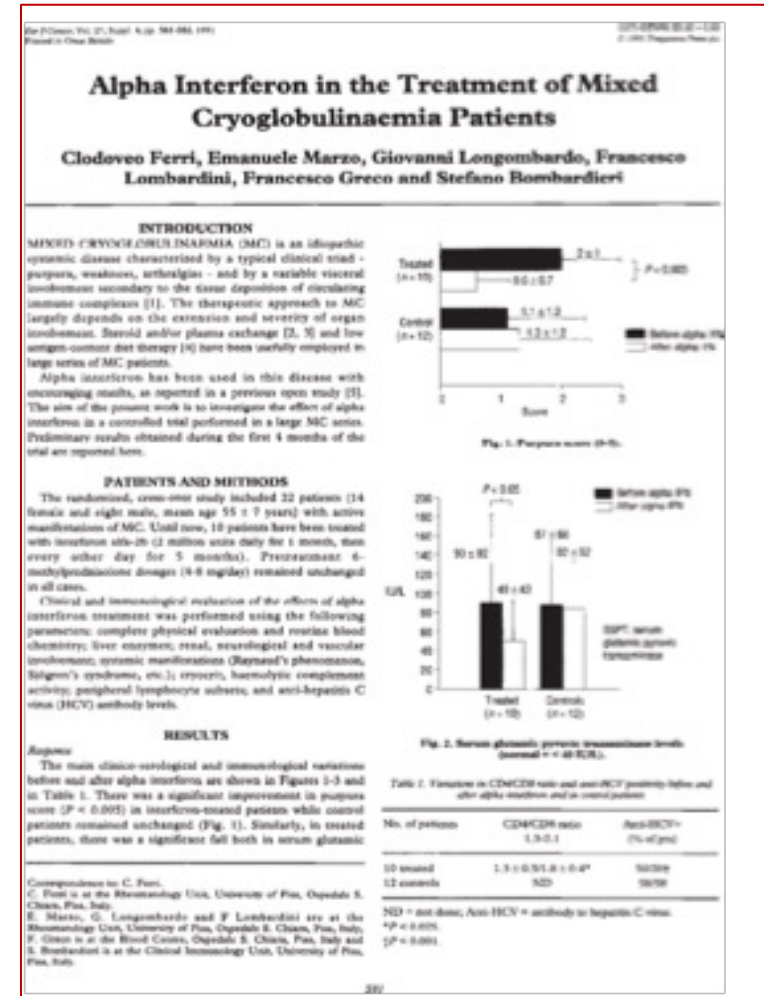
-**Ferri C et al**. Alpha-interferon in the treatment of mixed cryoglobulinemia patients. International Cancer Update.

Focus on Interferon Alfa 2b. Cannes, France.

**November 1-4, 1990.** Proceedings

(*Eur J Cancer* 1991; **27**: 81-82

DOI: 10.1016/0277-5379(91)90583-Y )



1991

**The two preliminary observations (1990) of increased prevalence of anti-HCV antibodies were confirmed on a larger case series of patients with MC**  
*Ferri C et al. A&R 1991*

1606

## BRIEF REPORT

**A**rthritis  
&  
**R**heumatology

**ANTIBODIES TO HEPATITIS C VIRUS IN PATIENTS WITH MIXED CRYOGLOBULINEMIA**

CLODOVEO FERRI, FRANCESCO GRECO, GIOVANNI LONGOMBARDO, PIERO PALLA, ADOLFO MORETTI, EMANUELE MARZO, PIER VITTORIO FOSELLA, GIAMPIERO PASERO, and STEFANO BOMBARDIERI

The prevalence of antibodies to hepatitis C virus (HCVAb) was investigated in 52 unselected patients with mixed cryoglobulinemia and in 84 patients with other systemic immunologic diseases. HCVAb were detected by an enzyme-linked immunosorbent assay, and their specificity was evaluated by a recombinant-based immunoblot assay. The presence of HBV-related markers was investigated in the same samples. HCVAb were found in 54% of mixed cryoglobulinemia patients, and the finding was confirmed by recombinant-based immunoblot assay in all cases. HCVAb and/or HBV markers were present in 70% of the patients. HCVAb seropositivity was significantly more frequent in mixed cryoglobulinemia patients with biopsy-proven liver involvement ( $P < 0.01$ ) and with increased serum transaminase levels ( $P < 0.01$ ). HCVAb were virtually absent in control patients with other immunologic diseases. These results support the notion that viral agents, i.e., HCV and possibly HBV, have a role in the pathogenesis of mixed cryoglobulinemia patients.

From the Rheumatology Unit and Clinical Immunology Unit, University of Pisa, and the Blood Center, Ospedale S. Chiara, Pisa, Italy.

Clodoveo Ferri, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Francesco Greco, MD: Ospedale S. Chiara; Giovanni Longombardo, BS: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Piero Palla, MD: Blood Center, Ospedale S. Chiara; Adolfo Moretti, MD: Blood Center, Ospedale S. Chiara; Emanuele Marzo, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Pier Vittorio Fosella, MD: Blood Center, Ospedale S. Chiara; Giampiero Pasero, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Stefano Bombardieri, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa.

Address reprint requests to Clodoveo Ferri, MD, Istituto di Patologia Medica I, Via Roma, 67, 56100 Pisa, Italy.

Submitted for publication November 29, 1990; accepted in revised form June 27, 1991.

Mixed cryoglobulinemia is a systemic disorder characterized by a typical clinical triad—purpura, weakness, and arthralgias—and by visceral complications such as liver and renal involvement (1). The pathogenesis of vascular and parenchymal injury in this disease can be related to deposition of circulating immune complexes (1,2); however, less information is available on the etiologic factor(s). Previous exposure to hepatitis B virus (HBV) in mixed cryoglobulinemia has been reported by some authors, though the prevalence of this association varies among the reports (1–3). Based on this association, it has been hypothesized that mixed cryoglobulinemia, like arthritis and polyarteritis (4,5), might be one of the extrahepatic manifestations of HBV infection. The finding of cryoglobulins in a variety of infectious diseases and the HBV seropositivity found in some mixed cryoglobulinemia patients support the possibility that mixed cryoglobulinemia may result from a number of types of infection in predisposed individuals. Since hepatitis C virus infection is responsible for a large proportion of non-A, non-B posttransfusion hepatitis and “autoimmune” chronic hepatitis (6,7), and since liver involvement is one of the most frequent manifestations of mixed cryoglobulinemia (1–3), we investigated the prevalence of anti-hepatitis C virus antibodies (HCVAb) and their correlation with clinical and serologic parameters in a large series of unselected patients with mixed cryoglobulinemia.

**Patients and methods.** Two hundred patients with mixed cryoglobulinemia were followed at the Rheumatology Unit of the University of Pisa between 1972 and 1990. Of these, 52 consecutive, unselected patients who attended the clinic for routine outpatient visits between March 1990 and October 1990 were

**1991**

**In the same year  
the first demonstration  
of a high prevalence (86%)  
of HCV infection (viremia)  
in patients with  
Mixed Cryoglobulinemia**

**Serum HCV RNA  
was assessed  
by polymerase chain reaction technique  
at Wellcome Diagnostics, London UK**

*Ferri C et al. Clin Exp Rheumatol 1991*

**Clin Exp Rheumatol 1991 Nov-Dec; 9(6): 621-4.**

## **Association between hepatitis C virus and mixed cryoglobulinemia**

C Ferri<sup>1</sup>, F Greco, G Longombardo, P Palla, A Moretti, E Marzo, A Mazzoni, G Pasero, S Bombardieri, P Highfield, Corbishley T

### **Abstract**

The prevalence of hepatitis C virus (HCV) RNA and of antibodies to HCV in an unselected series of 42 mixed cryoglobulinemia patients was investigated in this study.

**HCV RNA was detected by the polymerase chain reaction technique**, and HCV antibodies by two enzyme-linked immunosorbent assays (Chiron ELISA HCV, Second Generation, Emeryville CA, USA; Wellcome Diagnostic, England).

**HCV RNA was found in 86% of the mixed cryoglobulinemia patients.** Using either the Chiron ELISA or the Wellcome ELISA, HCV antibodies were present in 90% of the same samples; anti-HCVAb seropositivity was confirmed in all cases by immunoblot assay (Chiron RIBA HCV, Second Generation Assay).

A striking correlation between HCV RNA and anti-HCV antibody seropositivities was recorded. HCV RNA in mixed cryoglobulinemia patients was not correlated with the presence or absence of biopsy-proven liver involvement.

**These results suggest that the association between HCV and mixed cryoglobulinemia is not fortuitous, and therefore that HCV may have an etiopathogenetic role in this disorder.**

1992-93

An important step in the study of the etiopathogenetic role of HCV in autoimmune diseases (organ- and non-organ-specific) and in lymphoproliferative disorders was the

→ **discovery of HCV lymphotropism** (in addition to its well known hepatotropism) **demonstrated in either**

- Pts with isolated hepatitis C and
- Mixed Cryoglobulinemia pts

### Infection of peripheral mononuclear blood cells by hepatitis C virus.

Zignego AL, Macchia D, Monti M, Thiers V, Mazzetti M, Foschi M, Maggi E, Romagnani S, Gentilini P, Bréchet C. **J Hepatol. 1992 Jul; 15(3): 382-6.**

### Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia

C Ferri<sup>1</sup>, M Monti, L La Civita, G Longombardo, F Greco, G Pasero, P Gentilini, S Bombardieri, A L Zignego

**Blood 1993 Dec 15; 82(12): 3701-4.**

Clodoveo Ferri

Overview of the Research Line: from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis) to HCV infection, Autoimmunity, and Oncogenesis. 1972 -2024



## **Infection of Peripheral Blood Mononuclear Cells by Hepatitis C Virus in Mixed Cryoglobulinemia**

By Clodoveo Ferri, Monica Monti, Luca La Civita, Giovanni Longombardo, Francesco Greco, Giampiero Pasero, Paolo Gentilini, Stefano Bombardieri, and Anna Linda Zignego

A striking association between hepatitis C virus (HCV) infection and mixed cryoglobulinemia (MC) has been shown; thus, HCV seems to play an important etiopathogenetic role in this lymphoproliferative disorder. Because HCV is both a hepatotropic and lymphotropic virus, this study aimed to investigate the prevalence of HCV infection of peripheral blood mononuclear cells (PBMCs) in a series of 16 patients with type II (IgMk) MC. Antibodies against HCV were detected by commercially available kits (Second Generation Chiron enzyme-linked immunosorbent assay [ELISA] and recombinant-based immunoblot assay [RIBA]), and the presence of HCV RNA was evaluated in both sera and isolated PBMCs using the polymerase chain

reaction technique. A previous exposure to HCV was shown by ELISA and confirmed by RIBA in all cases (100%). Moreover, HCV RNA was present in the sera of 8 of 16 patients (50%), whereas its frequency markedly increased (13 of 16 [81%]) when genomic sequences were detected in peripheral lymphocytes. HCV RNA was never detected in the PBMCs of 20 control subjects. These findings showed that HCV infection, alone or in combination with other factors, may be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC, and may explain the appearance of a malignant non-Hodgkin's lymphoma in some subjects.

© 1993 by The American Society of Hematology.



*New England*

The knowledge acquired in the early nineties has led to

1991-1994

## Second key observation

1. *MC is frequently associated with HCV infection*
2. *HCV is a lymphotropic virus*
3. *MC can be complicated by B-NHL*

on the basis of which a question arose:

*What is the role of HCV  
in the etiopathogenesis  
of so-called 'idiopathic' B-NHL?*

*What is the role of HCV  
in the pathogenesis  
of so-called 'idiopathic' B-NHL?*

**1994**

## First description of the association HCV & B-cell Non-Hodgkin's lymphoma

In unselected series of patients with 'idiopathic' B-cell NHL referred to Hematology Unit of University of Pisa, Italy

HCV-related markers  
(anti-HCV/HCV RNA by PCR)  
were detected  
**in 34%**  
**of unselected B-NHL patients;**  
this prevalence is particularly  
significant when compared  
with HCV prevalence  
in Hodgkin's lymphoma (3%)  
and healthy controls (1.3%).

> [JAMA](#). 1994 Aug 3;272(5):355-6. doi: 10.1001/jama.1994.03520050033023.

**JAMA**  
The Journal of the American Medical Association

### Non-Hodgkin's lymphoma: possible role of hepatitis C virus

[C Ferri](#), [L La Civita](#), [F Caracciolo](#), [A L Zignego](#)

Br J Haematol

1994 Oct;88(2):392-4.

doi: 10.1111/j.1365-2141.1994.tb05036.x.

### Hepatitis C virus infection in patients with non-Hodgkin's lymphoma

[C Ferri](#)<sup>1</sup>, [F Caracciolo](#), [A L Zignego](#), [L La Civita](#), [M Monti](#), [G Longombardo](#),  
[F Lombardini](#), [F Greco](#), [E Capochiani](#), [A Mazzoni](#), et al.

**BJHaem** British Society for  
BRITISH JOURNAL OF HAEMATOLOGY **Haematology**

2002

In collaboration with  
Prof. AL Zignego  
Univ. of Florence, Italy

Demonstration of frequent  
activation of the proto-oncogene  
Bcl2 (t14; 18) translocation)  
in patients with  
MC with/without B-cell NHL

This finding supports the  
oncogenetic role of HCV  
and, at the same time,  
it strengthens the role of  
mixed cryoglobulinemia as  
pre-neoplastic condition

# Annals of Internal Medicine®

Articles | 1 October 2002

## Prevalence of *bcl*-2 Rearrangement in Patients with Hepatitis C Virus–Related Mixed Cryoglobulinemia with or without B-Cell Lymphomas

Anna Linda Zignego, MD, PhD ✉, Clodoveo Ferri, MD, Francesca Giannelli, PhD, Carlo Giannini, PhD, ... [See More](#)

**Clodoveo Ferri**  
Overview of the Research Line: from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis) to HCV infection, Autoimmunity, and Oncogenesis.  
1972-2024

**Keitaro Matsuo,<sup>1, 3, 5</sup> Aaron Kusano,<sup>3</sup> Aravind Sugumar,<sup>4</sup> Shigeo Nakamura,<sup>2</sup> Kazuo Tajima<sup>1</sup> and Nancy E. Mueller<sup>3</sup>**

<sup>3</sup>Department of Epidemiology, <sup>4</sup>Master of Public Health in Quality Improvement, University of Michigan, 615 Tappan Street, Ann Arbor, MI 48102-1115, USA

(Received May 27, 2004/Revised July 14, 2004/Accepted July

Studies on the  
**HCV & B-NHL**  
**association**  
published  
in the first 10 years  
following  
its first description  
in 1994

Abbreviations: ELISA, enzyme-linked-immunosorbent assay; EIA, enzyme-immunoassay; and RIBA, recombinant immunoblot assay. 2G and 3G stand for second generation and third generation, respectively.



*little lunch in Tuscany*



*1989 Summer*

1993

## European Journal of Clinical Investigation

First published: December 1993

<https://doi.org/10.1111/j.1365-2362.1993.tb00741>

### Study on **Etiopathogenetic role of HCV in patients with porphyria cutanea tarda through a possible virus-induced autoimmune mechanism**

In collaboration with prof.  
M. P. Manns immuno-hepatologist  
University of Hannover, Germany

## Hepatitis C virus-related autoimmunity in patients with porphyria cutanea tarda

C. FERRI, U. BAICCHI, L. LA CIVITA, F. GRECO, G. LONGOMBARDO,  
A. MAZZONI, G. CARECCIA, S. BOMBARDIERI, G. PASERO,  
A. L. ZIGNEGO, M. P. MANNS

### Abstract

Hepatitis C virus (HCV) infection is frequently found in autoimmune hepatitis and mixed cryoglobulinaemia. In these conditions HCV could be responsible for immuno-mediated organ alterations. The aim of this study was to evaluate the presence of immunological alterations in PCT patients, in which HCV infection has been frequently found. Twenty-three PCT patients were evaluated for clinical and serological alterations, including: chronic hepatitis, other systemic symptoms, serum cryoglobulins and rheumatoid factor (RF), haemolytic complement, serum immunoglobulins, anti-nuclear (ANA), anti-smooth muscle (ASMA), anti-liver-kidney-microsomal (anti-LKMI), anti-soluble-liver-antigen (SLA), anti-mitochondrial (AMA), anti-GOR antibodies, anti-HCV and HCV RNA. Abnormal serum ALT were present in the majority of cases (20/23, 87%), while liver biopsy revealed a chronic persistent hepatitis or chronic active hepatitis in 15/20 (75%) PCT patients. In a high percentage of subjects (91%) the presence of anti-HCV was detected by ELISA and RIBA II (Chiron, Emeryville CA, USA). In 17/22 (77%) cases the ongoing HCV replication in the serum was demonstrated by the detection of HCV genomes (polymerase chain reaction). The prevalence of both anti-HCV and HCV RNA in PCT was significantly higher if compared to 22 systemic immunological diseases ( $P < 0.001$ ) and 47 healthy subjects ( $P < 0.001$ ). A possible HCV-induced autoimmunity in PCT was suggested by the presence of the following immunological parameter alterations: anti-GOR in 13/23 (57%), ANA in 4/23 (17%), ASMA in 18/23 (78%), anti-LKMI in 1/23 (4%), RF in 23/23 (100%), mixed cryoglobulins in 4/23 (17/0), complement consumption in 10/23 (43%). The high prevalence of HCV infection and various immunological abnormalities suggest that HCV in combination with other factors (genetic, alcohol, etc.) could play a relevant role in the pathogenesis of hepatic and metabolic alterations of PCT.

**1999**

First demonstration of the  
association

**HCV infection  
and  
Papillary Thyroid Cancer**

JAMA, 1999 May 5;281(17):1588.

doi: 10.1001/jama.281.17.1588.

**Thyroid cancer in patients with  
hepatitis C infection**

[A Antonelli, C Ferri, P Fallahi](#)

PMID: 10235149

DOI: [10.1001/jama.281.17.1588](https://doi.org/10.1001/jama.281.17.1588)

**JAMA**  
The Journal of the American Medical Association

Studies  
on the relationship

# HCV infection & Endocrine Disorders

Rheumatology (Oxford), 2004 Feb;43(2):238-40.  
doi: 10.1093/rheumatology/keh011.

## Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients

[A Antonelli](#)<sup>1</sup>, [C Ferri](#), [P Fallahi](#), [M Sebastiani](#), [C Nesti](#), [L Barani](#),  
[R Barale](#), [E Ferrannini](#)

[Autoimmunity Reviews](#), 2008 Oct;8(1):18-23.  
doi: 10.1016/j.autrev.2008.07.017.

## Immunopathogenesis of HCV-related endocrine manifestations in chronic hepatitis and mixed cryoglobulinemia

[Alessandro Antonelli](#)<sup>1</sup>, [Clodoveo Ferri](#), [Silvia Martina Ferrari](#),  
[Michele Colaci](#), [Poupak Fallahi](#)

Studies  
on the  
relationship

**HCV  
infection  
&  
Endocrine  
Disorders**

**JAMA**  
The Journal of the American Medical Association

JAMA 2002 Aug 14;288(6):698-9.

doi: 10.1001/jama.288.6.698.

## Erectile dysfunction and hepatitis C virus infection

Clodoveo Ferri, Maria Antonella Bertozzi, Anna Linda Zignego

• DOI: [10.1001/jama.288.6.698](https://doi.org/10.1001/jama.288.6.698)



*Camargue*

**2015**

This review focused on  
the numerous  
clinical & laboratory studies  
on different  
HCV-related disorders  
following the first demonstration of  
HCV-associated MC & B-NHL

The complex of these  
organ and non-organ specific  
autoimmune disorders  
and lymphoproliferative/neoplastic  
conditions  
can be termed

**HCV syndrome**



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Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>  
DOI: 10.4254/wjh.v7.i3.327

*World J Hepatol* 2015 March 27; 7(3): 327-343  
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*REVIEW*

## **HCV syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer**

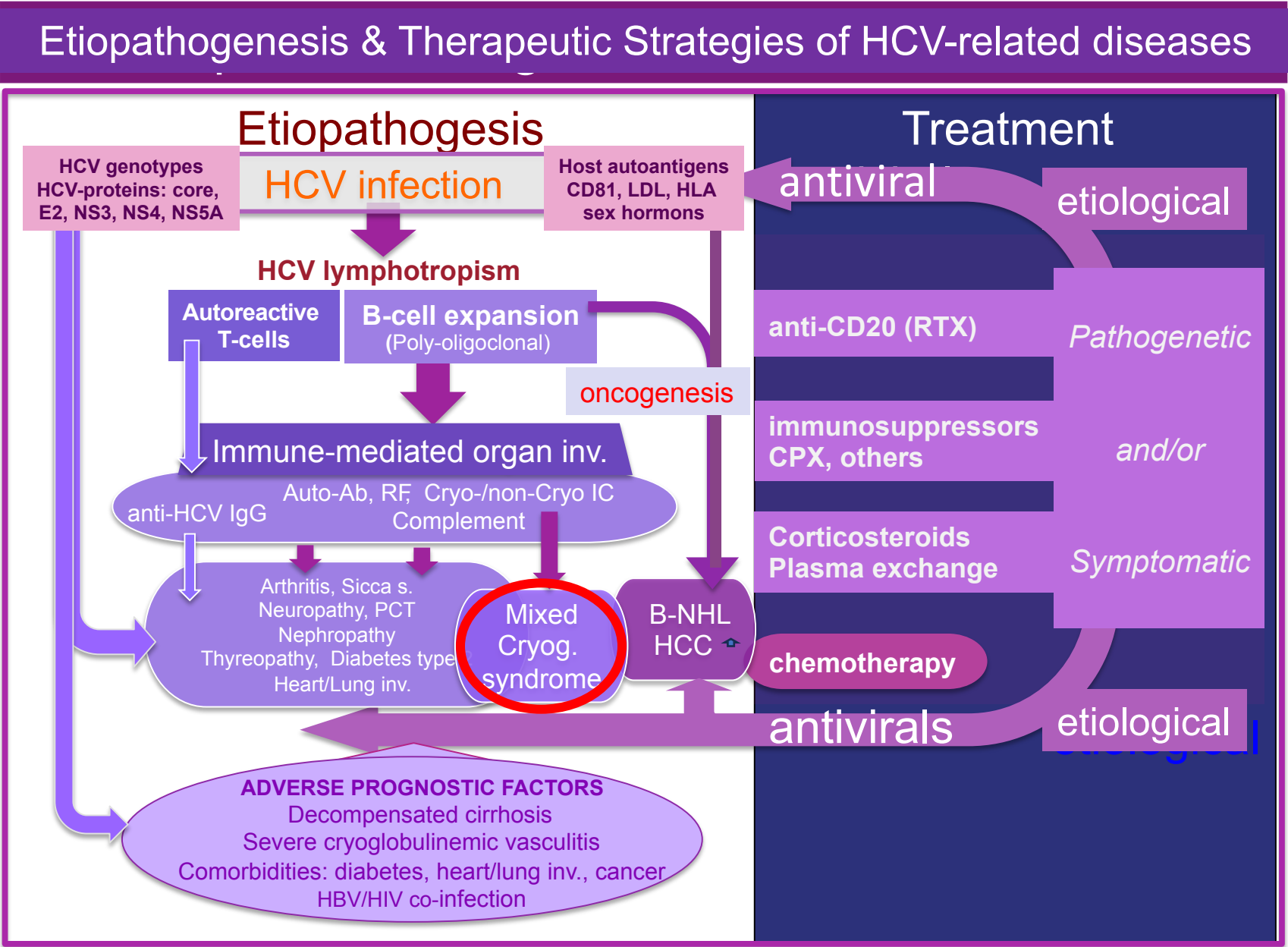
Clodoveo Ferri, Marco Sebastiani, Dilia Giuggioli, Michele Colaci, Poupak Fallahi, Alessia Piluso, Alessandro Antonelli, Anna Linda Zignego

2015

This review focused on  
the numerous  
clinical & laboratory studies  
on different  
HCV-related disorders  
following the first demonstration of  
HCV-associated MC & B-NHL

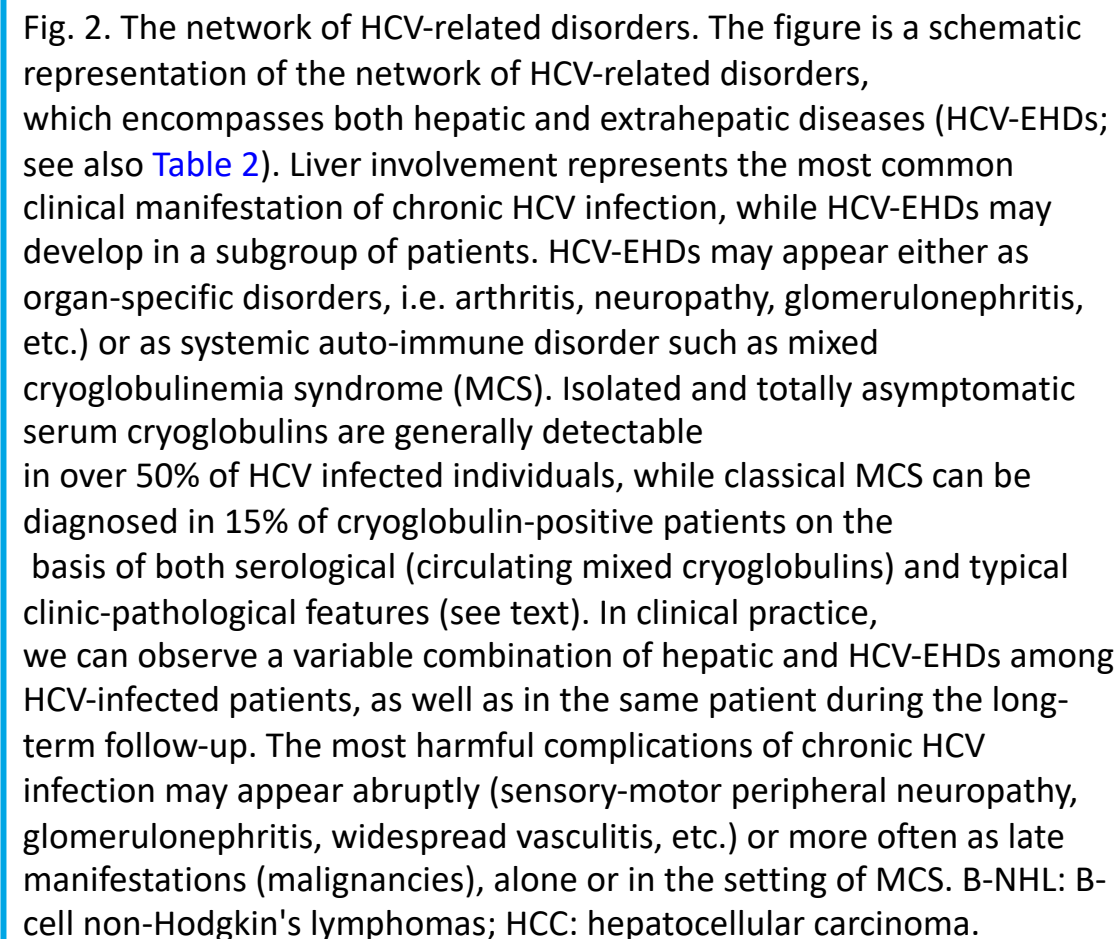
The complex of these  
organ and non-organ specific  
autoimmune disorders  
and lymphoproliferative/neoplastic  
conditions  
can be termed

**HCV syndrome**



**Mixed Cryoglobulinemia**

**a crossing road autoimmunity/linphoproliferation/cancer**



2021



# The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES ▾ TOPICS ▾ MULTIMEDIA ▾ CURRENT ISSUE ▾ LEARNING/CME ▾ AUTHOR CENTER PUBLICATIONS

CORRESPONDENCE

f X In

## Extrahepatic Manifestations of Chronic HCV Infection

Published June 30, 2021 | N Engl J Med 2021;385:94-96 | DOI: 10.1056/NEJMc2106143 | VOL. 385 NO. 1

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HCV in Autoimmunity & Oncogenesis

## Extrahepatic Manifestations of Chronic HCV Infection

**TO THE EDITOR:** In their recent review article, Cacoub and Saadoun (March 18 issue)<sup>1</sup> do not sufficiently highlight our pioneering research that led to the current definition of extrahepatic manifestations of hepatitis C virus (HCV) infection. A description of these pivotal studies might have provided beneficial insights.

In those studies, we found a striking association between HCV and mixed cryoglobulinemia syndrome, and the studies also showed the lymphotropism of HCV.<sup>2-4</sup> Mixed cryoglobulinemia syndrome is a multifaceted disorder that mimics most extrahepatic manifestations of HCV infection,<sup>2,4</sup> and chronic HCV infection may trigger multiple pathogenetic alterations that are respon-

sible for autoreactive, lymphoproliferative, and neoplastic disorders. HCV infection may exert an oncogenic role in B-cell non-Hodgkin's lymphomas as well as in hepatocellular carcinoma.<sup>5,6</sup>

The different phenotypes of extrahepatic manifestations of HCV infection may be the consequence of multistep and multifactorial pathogenetic processes. Both environmental and genetic cofactors may alter the disease progression from asymptomatic HCV infection to the most severe complications.

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University of Pisa  
Pisa, Italy

No potential conflict of interest relevant to this letter was reported.

1. Cacoub P, Saadoun D. Extrahepatic manifestations of chronic HCV infection. *N Engl J Med* 2021;384:1038-52.
2. Ferri C, Greco F, Longombardo G, et al. Association between hepatitis C virus and mixed cryoglobulinemia [see comment]. *Clin Exp Rheumatol* 1991;9:621-4.
3. Zignego AL, Macchia D, Monti M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. *J Hepatol* 1992; 15:382-6.
4. Ferri C, Monti M, La Civita L, et al. Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. *Blood* 1993;82:3701-4.
5. Ferri C, Caracciolo F, Zignego AL, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Br J Haematol* 1994;88:392-4.
6. Ferri C, Pileri S, Zignego AL. Hepatitis C virus, B-cell disorders, and non-Hodgkin's lymphoma. In: Goedert JJ, ed. *Infectious causes of cancer: targets for intervention*. Totowa, NJ: Humana Press, 2000:349-68.

DOI: 10.1056/NEJMc2106143

2022

## Autoimmunity Reviews

Volume 21, Issue 1,

January 2022

<https://doi.org/10.1016/j.autrev.2021.102923>

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# Effects of antiviral therapies in patients with HCV-related Cryoglobulinemic Vasculitis

## Predictors of long-term cryoglobulinemic vasculitis outcomes after HCV eradication with direct-acting antivirals in the real-life

[Laura Gragnani<sup>a</sup>](#), [Serena Lorini<sup>a</sup>](#), [Silvia Marri<sup>a</sup>](#), [Caterina Vacchi<sup>b</sup>](#), [Francesco Madia<sup>a</sup>](#), [Monica Monti<sup>a</sup>](#), [Clodoveo Ferri<sup>c 1</sup>](#), [Anna Linda Zignego<sup>a 1</sup>](#)

### Abstract

**Cryoglobulinemic vasculitis** (CV) is the most frequent extrahepatic manifestation during HCV-chronic infection. An effective Direct Acting Antiviral-treatment leads to CV clinical response in the majority of CV-patients although symptoms may persist/recur despite a sustained virological response. At present, no standardized clinical [predictive factors](#) for disease maintenance/recurrence were proposed, as emerged from a complete literature review we performed and reported. Here we provided a detailed descriptive analysis of a wide population of CV patients treated with DAA-based regimes and followed-up after therapy completion for longer than 72 weeks, in order to identify clinical or laboratory predictors of disease outcome and to optimize the patient management. Together with some baseline symptoms (neuropathy, weakness and sicca syndrome), two newly created scores, CV- and Global Severity Index, emerged as reliable and standardized tools to predict CV clinical response before initiating an antiviral therapy. In addition to predictive parameters previously proposed in the world literature, these novel Indexes could fill an unmet gap in the clinical management of the complex HCV-related CV.

2022

*Journal of  
Clinical  
Immunology*

**Impact of  
COVID19  
pandemic  
on  
patients with  
MC syndrome**

Journal of Clinical Immunology  
<https://doi.org/10.1007/s10875-023-01444-4>

ORIGINAL ARTICLE



# COVID-19 and Mixed Cryoglobulinemia Syndrome: Long-Term Survey Study on the Prevalence and Outcome, Vaccine Safety, and Immunogenicity

Laura Gragnani<sup>1</sup> · Marcella Visentini<sup>2</sup> · Serena Lorini<sup>1</sup> · Stefano Angelo Santini<sup>3,4</sup> · Gianfranco Lauletta<sup>5</sup> · Cesare Mazzaro<sup>6</sup> · Teresa Urraro<sup>7</sup> · Luca Quartuccio<sup>8</sup> · Fabio Cacciapaglia<sup>9</sup> · Piero Ruscitti<sup>10</sup> · Antonio Tavoni<sup>11</sup> · Silvia Marri<sup>1</sup> · Giuseppina Cusano<sup>2</sup> · Luisa Petraccia<sup>1</sup> · Caterina Naclerio<sup>7</sup> · Elena Treppo<sup>8</sup> · Giulia del Frate<sup>8</sup> · Ilenia Di Cola<sup>10</sup> · Vincenzo Raimondo<sup>12</sup> · Daniela Scorpiniti<sup>12</sup> · Monica Monti<sup>1</sup> · Lorenzo Puccetti<sup>11</sup> · Giusy Elia<sup>13</sup> · Poupak Fallahi<sup>14</sup> · Stefania Basili<sup>2</sup> · Salvatore Scarpato<sup>7</sup> · Florenzo Iannone<sup>9</sup> · Milvia Casato<sup>2</sup> · Alessandro Antonelli<sup>13</sup> · Anna Linda Zignego<sup>1</sup> · Clodoveo Ferri<sup>15,12</sup>

*the scientific community  
recognizes and expands  
the results of researches*

*masks*



Lecture  
HCV-MC & B-NHL

IMMUNOVASCULITIS  
from Molecular Pathology  
to Specific Therapy

Hamburg 2000, Germany

International Meeting of Experts  
of Systemic Vasculitides  
Churg J, Agnello V, Ferri C,  
Calabrese LH, Jannette JC,  
Savage C, Gross W

# IMMUNOVASCULITIS 2000 from Molecular Pathology to Specific Therapy

within

## 126. Kongress

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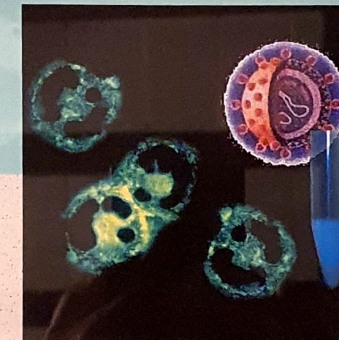
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5. FEBRUAR 2000

9.00 Uhr bis 13.00 Uhr

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Clodoveo Ferri (Pisa, Italy) – Leonard H. Calabrese (Cleveland, USA)

J. Charles Jennette (Chapel Hill, USA) – Caroline O. S. Savage (Birmingham, UK)

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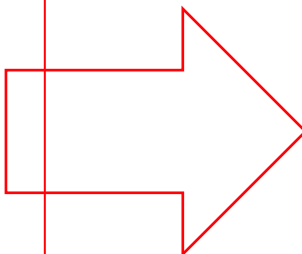
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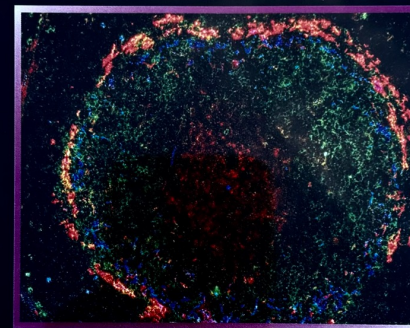
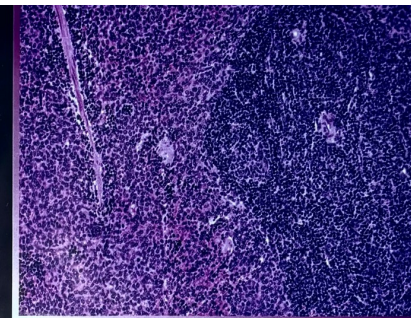
Lecture  
HCV infection & B-NHL

Congress on  
Cell of the Marginal Zone

National Institute of Allergy &  
Infectious Diseases  
National Cancer Institute  
Bethesda MD, USA  
April 2000



# Cells of the Marginal Zone



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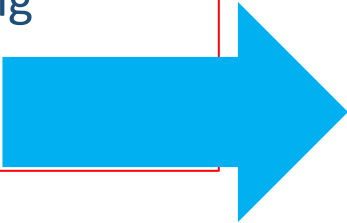
For more information contact Tiffany Mahone  
at [tmahone@iqsolutions.com](mailto:tmahone@iqsolutions.com)  
or call her at (301) 984-1471, x315

2001

Lecture  
HCV-MC & B-NHL

Association of Clinical Pathologists  
National Scientific Meeting

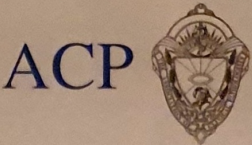
London UK



Association of Clinical Pathologists

189 Dyke Road Hove East Sussex BN3 1TL  
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*Certificate of Attendance*

This certificate confirms that

*Prof. Clodoveo Ferri, MD (invited speaker)*

attended the Association of Clinical Pathologists'

National Scientific Meeting

on

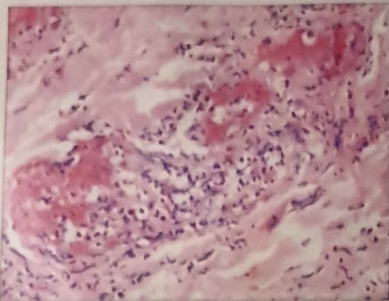
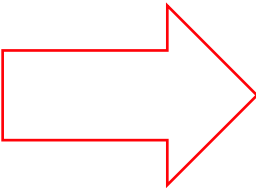
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at the Commonwealth Institute, Kensington, London

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*Bryan F Warren*  
Scientific Meetings Secretary

June 2001

2006



In severe necrotizing leukocytoclastic vasculitis, vast fibrinoid necrosis of the vessel wall and permeation by neutrophils occur.

## HCV: Key Target of Vasculitis Therapy

BY NANCY WALSH  
New York Bureau

AREND TERME, ITALY — The finding that the hepatitis C virus is implicated in the pathogenesis of cryoglobulinemic vasculitis means that therapy must address the chronic viral infection, the autoimmune dysregulation, and the potential for associated lymphoproliferative disorders, Dr. Clodoveo Ferri said at a congress on skin, rheumatism, and autoimmunity.

A linkage between hepatotropic viruses and cryoglobulinemia has been suspected for 3 decades, but only when hepatitis C virus (HCV) was identified was the causative connection made. In 1991, Dr. Ferri and his colleagues found a "striking correlation" among patients with mixed cryoglobulinemia and HCV seropositivity and also with hepatitis C viremia (Clin. Exp. Rheumatol. 1991;9:621-4). In Italy today 95% of cases of cryoglobulinemia are HCV related, said Dr. Ferri, chair of the Rheumatology department, University of Modena e Reggio Emilia Medical School, Italy.

The condition formerly termed "essential" mixed cryoglobulinemia is a leukocytoclastic vasculitis of small- and medium-sized vessels that manifests clinically with purpura, weakness, and arthralgias. Circulating

mixed polyclonal IgG and mono- or polyclonal IgM immunoglobulins are present, rheumatoid factor typically is positive, and C4 is low. Organ involvement results from deposition of immune complexes and complement.

The interplay between HCV infection and immune system abnormality is complex and may relate to a molecular mimicry mechanism involving certain HCV antigens and host autoantigens, with the result being B-lymphocyte activation and proliferation and autoantibody production (Curr. Opin. Rheumatol. 2006;18:54-63).

See Vasculitis page 16

### INSIDE



#### Manifestations of Asherson's

Tissue necrosis is a classic symptom of the disease.

PAGE 6

#### Dr. Dean Ornish: WHI Concerns

Low-fat diets could be harder to recommend.

PAGE 10



#### Preventing Rickets

Fortified milk may help fend off infant osteopenia.

PAGE 11

## Risks of Hormones Trump Benefits for Bones, WHI Finds

Protection seen for hip, vertebral fractures.

BY MITCHEL L. ZOLER  
Philadelphia Bureau

BETHESDA, MD. — The looming irony surrounding the hormone therapy study of the Women's Health Initiative was how wrong most experts had been about the potential benefits of estrogen in postmenopausal women.

Before the study, some had questioned the ethics of running a hormone therapy trial with a placebo arm. But almost 4 years after the early halt to the estrogen-plus-progestin arm of the Women's Health Initiative (WHI), the final-outcomes balance sheet shows many risks and few benefits. The second, estrogen-only arm of WHI ran a little longer and compiled better results, with the risks of treatment roughly equaling its benefits. But the bottom line for both forms of hormone therapy is that they are now recommended only for select clinical situations.

The major benefits were a reduction in hip and clinical vertebral fractures with both the estrogen-plus-progestin and the estrogen-only, and a reduction in the rate of invasive colorectal cancer in patients treated with estrogen plus progestin, said Dr. Marcia L. Stefanick, professor of medicine at Stanford (Calif.) University, speaking at a 2-day conference at the National Institutes

See Benefits for Bones page 21

## Natalizumab Indication for Rheumatoid Arthritis: No Go

BY ELIZABETH MECHCATTIE  
Senior Writer

GAITHERSBURG, MD. — The return of natalizumab to the market will not extend to its use in management of rheumatoid arthritis, according to a spokesperson for its manufacturer Biogen Idec.

The company has dropped its plans to pursue Food and Drug Administration approval of an indication for use of natalizumab (Tysabri) in the management of rheumatoid arthritis, the spokesperson said in an inter-

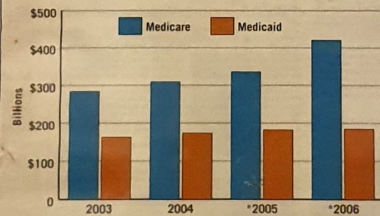
view. At its meeting last month, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended that natalizumab's return to the market for treating patients with relapsing forms of multiple sclerosis with the protective measure of having mandatory risk minimization plan in place to enhance clinical vigilance for early signs of progressive multifocal leukoencephalopathy.

The drug was taken off the market in February 2005 and ongoing trials in MS, rheumatoid arthritis, and Crohn's disease

See Natalizumab page 24

### VITAL SIGNS

#### Medicare Spending to Increase by 25% in 2006



\*Estimated costs.

Source: Health Affairs 2006;25:w61-w73

From Prof. R Heimann,  
anato-pathologist,  
President Eur. Soc. Pathology,  
back in 1971 he had observed  
at autopsy the **coexistence of**  
**lymphoma and cirrhosis**,  
the first disease was  
responsible for the patient's  
death, while the second one  
was not attributable to known  
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**This concomitance suggested**  
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Only after  
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(MC, cirrhosis, and B-NHL)  
**confirmed the previously**  
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**etiopathogenetic**  
**link:**

**Lymphoproliferation**  
**Liver cirrhosis**  
**Viral infection**

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Service d'Anatomie Pathologique  
Professeur R. HEIMANN

August 18,1995

Docteur R. GOTTLOB  
Docteur D. LARSIMONT

Consultants:  
Professeur A. VERHEST  
Docteur D. d'OLNE  
Docteur Z. HORANYI  
Docteur M. PETEIN  
Docteur N. RENARD

Professor Clodoveo Ferri  
Istituto Patologia Medica 1  
University of Pisa  
Pisa,Italy.

Dear Professor Ferri:

A colleague of mine drew my attention some months ago to the letter which  
you wrote to the J A M A and which appeared in August 1994.


Actually I am familiar with your previous work on mixed cryoglobulinemia  
and HCV but this letter delighted us specially because it backs up the  
concept of a link between viral hepatitis and some malignant lymphoproliferative  
disorders,concept which we put forward more than 20 years ago !.

In the meantime, a paper by Galun et al.appeared in the American Journal  
of Pathology involving HBV;this paper prompted us to write a letter to the  
editor of the Am.J.Pathol.

I enclose a copy of that letter and also a xerox of an old naive paper,the  
first one,which we wrote on that topic because I think it might amuse you.

With my best regards.

Sincerely yours.

  
Pr.R.Heimann.



EUROPEAN SOCIETY OF PATHOLOGY



OFFICE OF THE PRESIDENT  
Prof. Dr. R. HEIMANN  
Department of Pathology  
Academisch Ziekenhuis V.U.B.  
Laarbeeklaan 101  
B - 1090 Brussels - Belgium  
Tel : xx 32-2-477 5081  
Fax : xx 32-2-477 5085

5 February 1997

Professor Clodoveo Ferri  
Istituto de Patologia Medica 1  
Universita di Pisa  
Via Roma 67  
5600 Pisa, Italia  
Fax :00 39 50 550582

533 632

Dear Professor Ferri

Many thanks for your letter dated January 3. I really enjoyed reading your recent publications.  
I am also very impressed by the tremendous activity of your group.

You have no idea how pleased I am to find beautifully demonstrated in a modern and sophisticated way, the  
hypothesis which we crudely ventured more than twenty years ago.  
Anecdotally, I remember the kind words which an oncologist at the Cancer Institute, seated behind me during  
a CPC, whispered in my ear : « Heimann, avec tes cirrhoses et lymphomes, tu racontes des conneries ! »  
I am also impressed by the fact that the concept that some lymphoproliferative disorders could be related to  
Hepatitis C has been developped essentially if not exclusively in Italy .

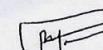
I just came back from a haematopathology course in San Diego, California where among others, I met Nancy  
Harris , one of the teachers and who is a well known haematopathologist at the Mass. General Hospital in  
Boston. I know her for many years. She was aware of our respective works and as matter of fact she alludes to  
the paper of Pozzato et al.( Blood 1994) in her chapter on low grade B-cell lymphomas in the recent (1996)  
monography on pathology of the lymphnodes edited by Lawrence Weiss and published by Churchill  
Livingstone .

So slowly but surely the concept that hepatitis viruses can induce lymphoproliferative disorders is gaining  
acceptance in the haematopathologists' community !

I thank you very much also for the offer to collaborate with you. Actually, I was chairman of the Department of  
Pathology at the Institut Jules Bordet until my retirement in October 1995 ; I am now consultant at the  
Department of Pathology of the Flemish Medical School and Academic Hospital ; I shall hold this full-time  
position until end of March and from then on, I shall remain consultant on a part-time basis. So I shall have  
plenty of time then . I would be delighted to collaborate with your team and would like to discuss with you  
how this could be done. Maybe we could meet for instance sometime in this coming spring or early summer at  
your best convenience ?.

In fact,my wife and I had planned to drive down to Rome and visit some close friends there.The date is still  
open and I would not mind taking the opportunity to visit you in Pisa. If you wish, I could even give a talk on  
the historical steps of our understanding of the relationship between liver diseases and lymphoproliferative  
disorders.

Looking forward to hearing from you and with my best regards, I am ,  
Yours sincerely,

  
R.Heimann

PS. I did not succeed  
in sending you this  
letter in a box.

Executive Committee 1995-1997

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Letters from Prof. R Heimann,  
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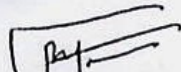
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Yours sincerely,

  
R.Heimann

PS. I did not succeed  
in sending you this  
letter as a fax .

## HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH

In this issue of Haematologica, Luppi and Torelli analyze the pathogenetic role of some lymphotropic viruses in human lymphoproliferative disorders.<sup>1</sup> This has been a field of active research in the last few years, and we should be proud of the fact that important investigations on the relationship between hepatitis C virus (HCV) and lymphoproliferative disorders have been performed in Italy. In addition, Torelli and coworkers have made important contributions to studies on herpesviruses.

The close association between HCV infection and mixed cryoglobulinemia (MC) represented the first evidence that this virus may have an etiopathogenetic role in lymphoproliferative disorders. Ferri *et al.*<sup>2</sup> investigated the prevalence of HCV infection of peripheral blood mononuclear cells in a series of 16 patients with type II mixed cryoglobulinemia. Previous exposure to HCV was shown in all cases (100%); moreover, HCV RNA was detected in peripheral lymphocytes from 13 out of the 16 patients, whereas it was never found in mononuclear blood cells from 20 control subjects. These findings strongly suggested that HCV infection might be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC.

Pozzato *et al.*<sup>3</sup> studied the clinical, histologic, and virologic findings of 31 patients affected with mixed cryoglobulinemia. The prevalence of anti-HCV antibodies was high (84%); polymerase chain reaction amplification of the 5' untranslated region of HCV was positive in 84% of subjects, and core region amplification was positive in 96%. A high prevalence of genotype II was found (77%), and chronic liver disease was present in 48% of patients. Bone marrow biopsy specimens showed the presence of low-grade non-Hodgkin's lymphomas in 12 cases (39%), whereas infiltration appeared to be reactive rather than monoclonal in 11 patients. This study confirmed that mixed cryoglobulinemia is closely associated with HCV infection since only

one patient was apparently not infected by the virus, and suggested that this disease is associated with a high prevalence of low-grade non-Hodgkin's lymphomas (NHLs).

The same authors investigated the long-term effects of  $\alpha$ -interferon on clinical, hematological and virological parameters in a group of 18 patients affected with type II mixed cryoglobulinemia.<sup>4</sup> A bone marrow biopsy was performed in all patients, and a liver biopsy was obtained in those with biochemical signs of chronic liver disease. All patients followed the same treatment schedule: three million units of recombinant interferon- $\alpha$  s.c., three times a week for 1 year. In 5 cases bone marrow histology showed the presence of a monoclonal lymphocytic infiltrate. Liver biopsies were performed in 13 (72%) of the patients and chronic liver disease was found in all 13. Anti-HCV antibodies were present in 17 (95%) subjects. HCV-RNA was detected in all cases (100%) before therapy. Five (28%) patients achieved a complete response and 9 (50%) a partial response, while the others (4 cases, 22%) showed minor responses. Four patients cleared the virus and obtained a complete remission of the MC. This study confirmed that HCV may be a cause of mixed cryoglobulinemia and suggested that  $\alpha$ -interferon may be an effective agent for the treatment of this disorder.

At this point Ferri *et al.* decided to investigate HCV infection in a series of 50 unselected Italian patients with B-cell NHL.<sup>5</sup> Antibodies against HCV were found in 30% of NHL, and HCV viremia in 32% of cases. HCV-related markers were detected in 34% (17/50) of NHL patients; this prevalence is particularly significant when compared with HCV seropositivity in Hodgkin's disease (3%) and healthy controls (1.3%). These data have been confirmed by Cavanna *et al.*<sup>6</sup>

Franzin *et al.*<sup>7</sup> investigated clonal expansions of IgM-producing B cells in 38 patients with a

chronic hepatitis C virus infection. Eight patients were affected with type II mixed cryoglobulinemia (two of whom also suffered from non-Hodgkin's lymphoma and one from Waldenström's disease), one with type III mixed cryoglobulinemia, one with Waldenström's disease, and 28 with chronic liver disease. Clonal Ig gene rearrangements were detected in all patients with type II mixed cryoglobulinemia, as well as at a high frequency (24%) in the HCV-infected patients without cryoglobulinemia. A polyclonal pattern was present in the patient with type III mixed cryoglobulinemia and in the 15 normal individuals and 16 age-related patients with HCV-negative alcoholic liver disease investigated as controls. The serum levels of rheumatoid factor were increased in all patients with a clonal expansion, suggesting that the expanded B-cell clones belong to the rheumatoid factor-producing B-cell subset.

De Vita *et al.* have reported for the first time localization of HCV within a parotid non-Hodgkin's lymphoma (NHL) lesion in the course of HCV-related type II essential MC, an important step toward implicating this agent in lymphomagenesis.<sup>8</sup> Plus and minus strand HCV RNA was first demonstrated by polymerase chain reaction on complete RNA from the lesion. Sialotropic viruses already shown to be involved in lymphoproliferation, ie Epstein-Barr virus and human herpesvirus-6, were absent from the same tissue lesion. According to the

current models of B-cell lymphomagenesis, a role for HCV as an exogenous antigenic stimulus should be considered for NHL development in the present case, whereas malignant B cells do not seem to permit active HCV replication.

These are just a few examples of the major contributions made by Italian science toward defining the pathogenetic role of HCV in lymphoproliferative disorders. The reader is referred to the review by Luppi and Torelli<sup>1</sup> for details.

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# 1996 Haematologica Editorial HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH



*Naca*

# ABSTRACTISSIME 92



Les Best d'Abstract Rhumato (p. 7).

## ABSTRACT

### RHUMATO

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1992

After the first demonstration of the association HCV-MC (1991)

**Q** uatre-vingt-treize. Est-ce une révolte décrite par une plume hugolienne ? Non, lecteurs, c'est une révolution (terrestre !). La prochaine. Abstract Rhumato s'y prépare, jetant ses troupes les plus valeureuses dans le dernier combat de 1992, le quatre-vingt-quatorzième depuis qu'il va au feu. Clodoveo Ferri a été désigné pour partir en éclaireur. On ne pouvait mieux choisir que ce condottiere pisan pour débûser le virus de l'hépatite C camouflé dans le maquis des cryoglobulinémies (Le Lauréat, page 5). Mais voici en seconde ligne les meilleurs du bataillon d'articles, de ceux qu'on distingue et qu'on décore de lauriers pour avoir au milieu de tant d'autres papiers mené la charge d'Abstract Rhumato pendant toute cette année que nous disions presque révolue (Les Best, page 7). Mais où en sont les alliés ? C'est-à-dire les rhumatologues du reste de l'Europe... Qu'on ne s'y trompe pas ! Ici ou de l'autre côté des ci-devant frontières, c'est le même combat (Rhumato sans frontières, page 14). Plus loin, les autres corps d'armée (cardiologues, neurologues, psychiatres, gastro-entérologues, pédiatres, dermatologues, gynécologues...) se sont réunis pour parler de la stratégie de leurs propres combats. Faites circuler le mot de passe (Médicoscopie, page 22)... Cependant, les négociations se poursuivent à l'arrière. Vérifiant plus que jamais l'adage "la guerre est décidée par ceux qui ne la font pas", ministres de la santé, directeurs de caisse et présidents des syndicats professionnels en sont encore aux Grandes Manœuvres malgré plusieurs plans de batailles successivement avalisés puis rejetés. Il n'y aura pas en 92 de Convention nationale... nonobstant les accords historiques (Profession santé, page 27). Bref, il n'est que temps de nous accorder une trêve. Celle de Noël par exemple.

Marie-Line Barbet

## LE LAURÉAT

Si ces résultats se trouvent confirmés, le nombre des CGM dites essentielles devrait donc singulièrement diminuer. Reste que les mécanismes physiopathologiques qui pourraient expliquer la relation entre VHC et CGME ne sont pas encore totalement éclaircis. Selon notre chercheur italien "le VHC, mais également à un moindre degré le VHB ou d'autres virus inconnus, pourrait provoquer un trouble lymphoprolifératif

responsable de la production de facteur rhumatoïde et de taux élevés de complexes immuns circulants (CIC) incluant les cryoglobulines, ces dernières étant responsables de lésions vasculaires à l'origine des différentes manifestations cliniques". De plus, "une altération de la clairance des CIC par les cellules de Küppler peut contribuer à maintenir des taux sériques élevés de cryoglobulines potentiellement toxiques".



Clodoveo Ferri, chercheur chaleureux pour une affection froide.

### Gros plan sur les cryo

Les cryoglobulines (GC) sont des immunoglobulines qui précipitent au froid et se redissolvent à 37 °C. On distingue :

- Des CG monoclonales (type I) qui sont formées d'un composant monoclonal, le plus souvent IgM.
- Des CG mixtes à composant monoclonal (type II) qui correspondent à des complexes immuns comprenant une immunoglobuline monoclonale (le plus souvent une IgM) et une immunoglobuline polyclonale, généralement une IgG, le premier constituant exerçant une activité rhumatoïde ou anti-idiotypique contre le second.
- Des CG mixtes polyclonales (type III) constituées d'immunoglobulines polyclonales comprenant, le plus souvent, une IgM polyclonale à activité anti-IgG (facteur rhumatoïde).

Les CG de type I sont responsables des tableaux les plus sévères liés à l'hyperviscosité plasmatique et/ou à leur précipitation intravasculaire. Les CG mixtes, surtout de type II, provoquent une vascularite par dépôt de complexes immuns circulants avec classiquement asthénie, arthralgies, purpura et parfois anomalies hépatiques. Les CG mixtes de type III sont souvent asymptomatiques.

Les causes des CG sont multiples. Les CG monoclonales sont surtout observées au cours des lymphomes et des hémopathies. Les CG mixtes sont essentiellement constatées au cours d'affections auto-immunes ou infectieuses. Dans 18 à 30 % des cas, aucune cause ne peut être retenue : la CG est dite essentielle.

Pour l'instant il est cependant impossible à C. Ferri de confirmer la possible séquence : infection par le VHC - hépatite chronique - cryoglobulinémie. Mais il précise cependant que "le suivi de plus de 200 cas de CGM montre que pour 20 % des dossiers, l'hépatite précède les manifestations typiques de la CGM (purpura, asthénie, arthralgies, neuropathie périphérique, néphropathie, ulcérations cutanées). Dans 48 % des observations, l'hépatite apparaît au cours de l'évolution de la maladie alors que dans 32 % des cas, une atteinte clinique hépatique manifeste n'est pas détectable ; la prévalence du VHC étant dans ce dernier cas comparable à celle observée pour la totalité des CGM".

Cependant la plupart des études réalisées incluaient de nombreux patients porteurs d'anomalies hépatiques. Y aurait-il là un biais ? Apparemment pas pour notre rhumatologue pisan qui avance que "la même prévalence des marqueurs du VHC constatée dans le groupe des patients n'ayant aucun signe clinique ni sérologique d'hépatite indique clairement que le VHC, qui est un virus à la fois hépatotrope et lymphotrope, est responsable de perturbations immunologiques plus complexes".

Plus encore, une fréquence élevée d'infection par le VHC ayant été rapportée dans les hépatites chroniques auto-immunes, C. Ferri et ses collaborateurs font l'hypothèse d'un mécanisme étiopathogénique commun aux CGM et aux hépatites chroniques auto-immunes.

### Un traitement à l'épreuve

Plusieurs équipes ont tenté de traiter les CGME par interféron (IFN) alpha avec un certain succès. C. Ferri propose cette modalité thérapeutique chez les patients ayant une infection à VHC manifeste et une maladie active, en général avec vascularite cutanée et hépatite.

De plus, il propose "une personnalisation des modalités thérapeutiques, à savoir de la dose et de la durée du traitement, suivie par une diminution lente de l'IFN alpha afin d'éviter un phénomène de rebond, un critère d'exclusion important étant la présence d'une neuropathie périphérique sévère".

Les jours prochains seront donc encore laborieux pour ce clinicien infatigable, mais on peut l'espérer, riches en découvertes. Décidés à mieux cerner le rôle du VHC dans la CGM et les relations entre l'hépatite des CGM et l'hépatite chronique auto-immune, C. Ferri et son équipe aimeraient aussi étudier les possibilités d'évolution des CGM en lymphome malin et le rôle de l'infection par le VHC dans ce phénomène.

Patricia Thelliez

2000

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## Hepatitis C Virus, B-Cell Disorders, and Non-Hodgkin's Lymphoma

Clodoveo Ferri, Stefano Pileri, and Anna Linda Zignego

### HEPATITIS C VIRUS INFECTION

Since its identification in 1989 (1,2), hepatitis C virus (HCV) has been recognized as the major causative agent of posttransfusion and sporadic parenterally transmitted non-A–non-B hepatitis (3). HCV is a single-stranded, positive-sense RNA virus showing similarities of genomic organization with pestiviruses. The introduction of second- and third-generation enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay (RIBA) tests significantly improved the diagnostic procedures for the detection of HCV-related antibodies (anti-HCV). Unlike many other viral infections, the detection of serum IgG class antibodies often suggests active HCV infection. However, anti-HCV may persist long after viral clearance. Thus, detection of viral RNA sequences using polymerase chain reaction (PCR) or other amplification methods is required to demonstrate infectious HCV (4). In patients with non-A, non-B hepatitis there is generally a good concordance between anti-HCV and PCR results. The detection of HCV RNA sequences in tissue specimens by *in situ* hybridization could be usefully employed mainly for etiopathogenetic investigations, although this still requires proper validation (5).

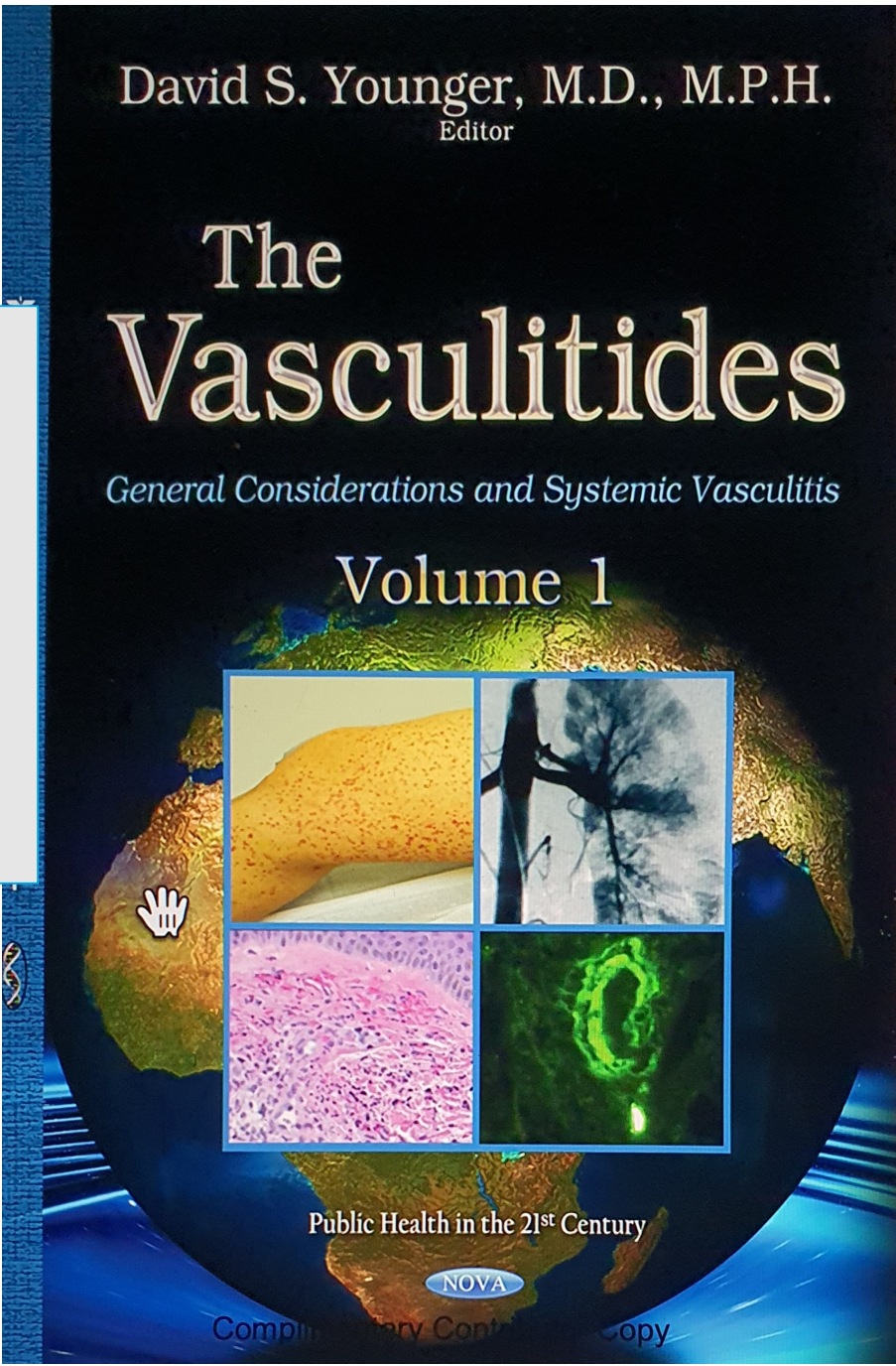
HCV genotypes have been defined by means of nucleotide and amino acid sequence analyses. There is an increasing number of HCV types and subtypes; at least 6 major HCV genotypes with 11 subtypes have been demonstrated in patient populations from different geographic areas (6). The presence of different HCV genotypes seems to be relevant for both pathogenetic and therapeutic implications, as suggested by the increased prevalence of genotype 1b in subjects with low response to interferon treatment and genotype 2a/c in lymphoproliferative disorders (3–8). Although some HCV genotypes are prevalent in particular geographic areas, a large variety of types and subtypes appears in a given country. In addition, HCV shows marked genetic variability. The viral genome is a mixture of heterogeneous HCV RNA molecules, often designated as quasispecies (9). The coexistence of multiple mutants provides an efficient and rapid mechanism for the virus to escape the immune response and therefore to persist in the host. The large majority of infected individuals develop chronic HCV infection (3,10), with about 70% showing chronic hepatitis.

2014

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Chapter 12

Cryoglobulinemic Vasculitis

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Abstract

Cryoglobulinemic vasculitis, also termed mixed cryoglobulinemic syndrome, is a rare systemic small vessel vasculitis due to the vascular deposition of immune-complexes, mainly mixed IgG-IgM cryoglobulins. It is associated with hepatitis C virus infection, immunological, and neoplastic diseases. Cryoglobulinemic vasculitis is characterized by the classical triad of purpura, weakness and arthralgia, frequent multiple organ involvement, and with infrequent late lymphatic and hepatic malignancies. The etiopathogenesis of cryoglobulinemic vasculitis is not completely understood. However, hepatitis C viral infection and associated lymphotropism, genetic and environmental factors play important roles in cryoglobulin and immune-complex production that deposit in blood vessels, and in B-lymphocyte expansion. The diagnosis is suggested by clinical evidence of purpura, circulating mixed cryoglobulinemia and low C4 levels, and pathologically evident leukocytoclastic vasculitis in skin biopsy lesions. The prognosis is poor in patients with renal disease, liver failure, and malignancy. Treatment is directed toward eradicating hepatitis C viral infection employing combination PEGylated-interferon-alpha and ribavirin treatment, immunomodulatory and immunosuppressant medications as warranted by the level of clinical severity.

Introduction

Cryoglobulinemic vasculitis (CV) is a small vessel vasculitis (SVV) due to the vascular deposition of cryoprecipitable or non-cryoprecipitable immune-complexes (IC) and complement [1]. Cryoglobulinemia and cryoimmunoglobulinemia are interchangeable terms

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Chapter  
*Cryoglobulinemia  
and HCV*

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Cryoglobulinaemia and  
Hepatitis C Virus

Clodoveo Ferri, Marco Sebastiani, David Saadoun,  
Patrice Cacoub

A previous version was coauthored by Clodoveo Ferri, Maria Teresa Mascia,  
David Saadoun and Patrice Cacoub

Learning objectives:

- Correctly classify/diagnose cryoglobulinaemia and mixed cryoglobulinaemia (MC)
- Use the correct technical procedures to detect and characterise cryoglobulin
- Describe and explain the main mechanisms involved in the aetiopathogenesis of MC syndrome
- Outline the epidemiology, prognosis and main clinical manifestations of MC syndrome (cryoglobulinaemic vasculitis)
- Make a differential diagnosis between MC syndrome and other autoimmune rheumatic disorders (Sjögren's syndrome, rheumatoid arthritis, other systemic vasculitides)
- Define the main organ and systemic autoimmune disorders possibly triggered by hepatitis C virus (HCV) infection
- List the possible neoplastic complications correlated with HCV infection
- Describe and explain the pathogenetic mechanisms of HCV-related autoimmune and lymphoproliferative disorders
- List the main targets of HCV-mixed cryoglobulinaemia therapy: clinical response (organ target manifestations), virological response (HCV RNA) and immunological response (cryocrit, C4 serum level)
- Understand that antiviral therapy (Peg-interferon  $\alpha$  plus ribavirin) is the cornerstone of HCV-mixed cryoglobulinaemia treatment
- Recognise that HCV viral load correlates with clinical outcome
- Know that B cell depleting therapy (rituximab) is an interesting additional therapeutic option
- Explain the timing of action and the limitations of rituximab
- Explain concerns about immunosuppressant agent use in HCV-mixed cryoglobulinaemia
- Describe the use of steroids immunosuppressant agents and plasmapheresis

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*The wind blows at noon,  
then turns to the north;  
it turns and turns  
and above its turns  
the wind returns*

*Vanity of vanities,  
says Qohelet.  
Vanity of vanities,  
all is vanity!*